REMARKS

This is in response to the Office Action transmitted October 10, 2008. The claims are as previously filed.

Enclosed for the Examiner's convenience is a copy of the journal article entitled, "Molecular Interactions on Microarrays" (Southern et al., *Nat. Genet.* 1999 Jan(1 Suppl):5-9). Applicant refers below to this article as evidence supporting nonobviousness of the claimed invention.

Claims 44-52 and 55 will be pending following entry of this Response.

Entry of this Response is respectfully requested.

The Rejections Under § 103(a)

I. The Rejection of Claims 44-48, 50-52 and 55 Under § 103(a)

Claims 44-48, 50-52 and 55 have been rejected under 35 U.S.C. § 103(a) over the combined disclosure contained in the following six references: *Biotechniques* 29:530-536 (2000) ("**Ohyama**" hereafter) as evidenced by *Nat. Biotechnol.* 15:1359-1367 (1997) ("**Wodicka**" hereafter), *Biotechnol. Prog.* 11:393-396 (1995) ("**Marble**" hereafter), U.S. Pat. No. 6,060,288 ("**Adams**" hereafter), U.S. Pat. No. 6,310,354 ("**Hanninen**" hereafter), and *Nucl. Acids Res.* 26:2224-2229 (1998) ("**Majlessi**" hereafter). The reasoned logic of the rejection has been made of record, but essentially alleges the obviousness of modifying the high-density oligonucleotide array of the primary and secondary references to include an immobilized T7 promoter-primer. Applicant respectfully traverses the rejections for the following reasons.

A. Proposed Modification Renders Prior Art Unsatisfactory for Intended Purpose

The pending claims cannot be considered obvious under § 103(a) by the reasoning in the Office Action because the suggested modification inappropriately renders the primary prior art reference unsatisfactory for its intended purpose. (*see* M.P.E.P. § 2143.01) **Ohyama** discloses devices and procedures intended for the generation of nucleic acids "suitable for hybridization of high-density oligonucleotide arrays for gene expression profiling" (*see* Abstract). In accordance with the teaching of **Ohyama,** *in vitro* transcripts must undergo a chemical cleavage step to reduce their lengths following synthesis, but prior to hybridization. This naturally requires physical separation of (1) the T7 promoter-primer used for creating cDNA templates, and (2) probes immobilized on the high-density oligonucleotide array. Combining the probe and primer on the same surface of a solid support bead would defeat the purpose of the physical separation disclosed by **Ohyama.**

Indeed, **Ohyama** as evidenced by **Wodicka** clearly defines a device and procedure that requires physical isolation of the RNA synthesis reaction and the probe hybridization reaction to achieve the intended purpose. **Ohyama** teaches ultimately synthesizing double-stranded cDNA using a T7 promoter-primer and nucleic acid isolated from a biological sample for first-strand synthesis (*see* pages 531-532, under "Target Sample Preparation"). The resulting cDNA was then purified and used to synthesize biotinylated RNA (*see* page 532, first full paragraph of col. 2) using a commercially available kit. The biotinylated RNA was purified using an RNeasy® kit from Qiagen, and fragmented down to 30-50 nts before hybridizing to unlabeled probes (*i.e.*, 25-mers) in a microarray format. Unhybridized material was removed by washing, and the hybridized fragments detected using fluorescently labeled streptavidin protein. Like **Ohyama, Wodicka** teaches these essential steps, including chemically fragmenting the biotinylated RNA to increase hybridization efficiency and specificity. Indeed, **Wodicka** states under col. 1 on page 1360:

> "Prior to hybridization, the RNA samples were fragmented to increase hybridization efficiency and specificity, and to reduce potential problems caused by nucleic acid secondary structure."

The importance of the probe fragmentation step to microarray technology has been addressed by Southern et al., in the enclosed article entitled, "Molecular Interactions on Microarrays" (*Nat. Genet.* 1999 Jan; 21(1 Suppl): 5-9). With regard to RNA probes, Southern states on page 8 (*i.e.*, under "Minimizing Secondary Structure of Targets"):

> "However, RNA has stable secondary structure which can interfere with hybridization, as we have seen. Steps must be taken to reduce these effects, such as fragmenting the RNA, preferably to a size close to that of the oligonucleotides on the array." [Emphasis added]

Consistent with this guidance, both **Ohyama** and **Wodicka** instruct steps for (a) synthesizing biotinylated RNA, (b) fragmenting biotinylated RNA, and (c) hybridizing the biotinylated and fragmented RNA to a high-density oligonucleotide array (*i.e.*, these steps taking place under different reaction conditions).

The suggested obvious modifications to the primary reference render it inappropriate for generating probes "suitable for hybridization of high-density oligonucleotide arrays." Simply stated, the instantly claimed device would not permit the necessary synthesis, fragmentation, and subsequent purification of *in vitro* transcripts prior to contact with immobilized probe. "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." (*See* MPEP § 2143.01, citing *In re Gordon*, 773 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)) Accordingly, Applicant requests withdrawal of the § 103 rejection of Claims 44-48, 50-52 and 55.

B. Rejection Improperly Relies on Combining References Where Reference Teaches Away from Their Combination

Another reason the rejection is improper is because there is a requirement for combining references where the references teach away from each other. **Ohyama** as evidenced by **Wodicka** discloses a device comprising an array of unlabeled hybridization probes, and instructs methods dependent on physical separation of the array and T7 promoter-primers. The references specifically instruct hybridization of RNA that has been chemically fragmented between the time of synthesis and hybridization to the array. The fragmentation step is purposeful (*see* **Ohyama** as evidenced by **Wodicka**, and Southern et al.), and is only possible because of the separation of the RNA-synthesizing and RNA-hybridizing reactions. **Marble** teaches synthesizing RNA transcripts using a bead-immobilized template for the purpose of illustrating a reusable source of *in vitro* transcripts (*see* Abstract). According to **Marble**, newly synthesized transcripts purposely enter the solution-phase and separate from the reusable device comprising the template bound to the solid support. Indeed, the virtue of RNA synthesized by the method and device of **Marble** is its ability to separate from the solid support on which is was synthesized. **Adams**, whose intended purpose is completely opposite **Marble**, instructs devices and methods for preventing amplicons from separating away from a solid support, thereby reducing carry-over contamination between different amplification reactions. According to the interpretation of **Adams** set forth in the Office Action, the opposite strand primer taught by **Adams** is a "probe," meaning that **Adams** "detects" only full length amplification products (*i.e.*, primer extension products having at their terminus a binding site for the "probe," which is actually the opposite-strand primer). Fragmenting the amplicon of **Adams** in accordance with the principle of operation employed by **Ohyama** as evidenced by **Wodicka** would be contraindicated, since the "probe" binding sequence of **Adams** is identical to the "primer" binding site, and since only full length primer-extension products can serve as amplification templates. **Hanninen** instructs a device and approach for distinguishing (a) hybridized polynucleotide probe that has become bound to a bead, from (b) unhybridized polynucleotide probe that remains free in solution-phase, without having to separate

these two species from each other. The method depends on recruiting detectable label from the solution-phase onto the bead, where the label becomes concentrated. Two-photon fluorescence excitation is then used for detecting immobilized probe among the background of unhybridized probe. Insofar as hybridization probes are concerned, **Hanninen** requires a detectably labeled probe that partitions between the solution phase and the solid phase. In this respect, **Hanninen** is incompatible with a system wherein the labeled hybridization probe does not partition between the different phases. **Majlessi** merely discloses the virtue of probes comprising particular nucleotide analogs, and provides no suggestion that would lead an ordinary skilled artisan to undo the essential teachings of the remaining references and combine them to result in the suggested obvious device.

The instantly claimed invention cannot be considered obvious under § 103, because the suggested references never would have been combined by one of ordinary skill in the art. For example, **Ohyama** as evidenced by **Wodicka** teaches fragmentation of RNA following synthesis, and prior to contact with immobilized probe. The fact that **Ohyama** actually benefits from maintaining the RNA synthesizing and hybridizing reactions separate from each other would not lead the ordinary skilled artisan to defy that teaching and employ the immobilized T7 promoter-primers of **Marble** on the same surface as the immobilized probes. Moreover, **Marble** and **Adams** specifically conflict with each other because one seeks to produce synthetic nucleic acids that separate from a solid support, while the other guides against that approach and seeks to produce synthetic nucleic acids that remain attached. As well, by the logic expressed in the Office Action, **Adams** would require full length *in vitro*-synthesized nucleic acids for detection, but this is in conflict with the requirement of the primary reference for chemical fragmentation that precedes probe hybridization. Likewise, **Hanninen** guides the use of labeled hybridization probes that partition between the solution-phase and the immobilized-phase. This would not lead the ordinary skilled artisan to forego this key teaching and require immobilized probes in accordance with **Adams** prior to contact with any nucleotide polymerizing enzyme. It is improper to combine references where the references teach away from their combination. (*See* M.P.E.P. §

2145(X)(D)(2)) Accordingly, Applicant believes the rejection is improper, and so requests withdrawal of the § 103 rejection of Claims 44-48, 50-52 and 55.

C. Proposed Modification Inappropriately Changes the Principle of Operation of Prior Art

The invention defined by the instant claims cannot be considered obvious under § 103 because the proposed modification inappropriately changes the principle of operation of the underlying prior art. **Ohyama** as evidenced by **Wodica** relies on a principle of operation wherein RNA synthesis and hybridization reactions are isolated from each other. By this approach, *in vitro* transcribed RNA can be separated from all reagents used in the synthesis reaction, and then fragmented prior to contact with an array of immobilized probes. **Marble** teaches RNA transcription initiated from a bead-immobilized T7 promoter-primer, but never suggests retaining and detecting transcription products on the same bead. Indeed, the principle of operation underlying the reusable bead format of **Marble** requires that *in vitro* transcripts separate from the solid support bead, and not be retained (*e.g.*, by a hybridization probe separate from the template). The principle of operation underlying **Adams** requires that amplification products remain attached to the bead to reduce sample-to-sample carryover contamination known to plague PCR procedures (*see* Background). This is the opposite from the suggested obvious device, wherein synthetic RNA enters the solution-phase. The principle of operation underlying **Hanninen** requires recruiting and concentrating a fluorescent label onto the surface of a microparticle (*e.g.*, by capturing enzymatically synthesized amplicons comprising the label), and then detecting the captured label while substantially ignoring free label in solution (*e.g., see* col. 2 at lines 65-67; col. 3 at lines 4-6; and col. 3 at lines 53-57). In the paragraph bridging columns 10-11, **Hanninen** summarizes:

> "The microphotometric measurement system used for the device of this invention can distinguish optically between the fluorescence emitted from the surface of the microparticles and the fluorescence emitted from the solution surrounding the microparticles. This resolution capability is based on the fact that in an appropriately diluted reaction suspension, only one microparticle at a time fits in the focal volume. The microparticles concentrate the fluorescently labeled nucleic acid sequences and the concentration of the labels in terms of mole/l in the microscopic volume of the microparticle is many order of magnitude higher than that of the free label molecules in the suspension. Consequently the background signal caused by free, labeled nucleic acid sequences is minimal." [Emphasis added]

According to **Hanninen**, "the crucial point of [the] invention is the use of two-photon excited fluorescent signal to detect the formation of nucleic acid amplification products," and measurement of fluorescent emissions from single microparticles when they randomly float through the restricted focal volume of a two-photon exciting laser beam (*see* col. 5 at lines 42-48). If the probes of **Hanninen** had been labeled and immobilized in the absence of analyte nucleic acid, then there would have been no reason to employ the "crucial" two-photon excitation system because it would be unnecessary to distinguish the nonexistent "free label molecules in the suspension." Thus, the principle of operation is changed here, too. **Majlessi** simply teaches that 2'-methoxy oligonucleotide probes are particularly advantageous when used for detecting RNA targets, and provides no reason to modifythe principle of operation underlying the remaining references.

The suggested obvious modification inappropriately changes the principle of operation underlying the prior art, and cannot properly defeat patentability of the instantly claimed invention. More specifically, the suggested obvious device requires changing the principle of operation underlying **Ohyama** as evidenced by **Wodicka** by eliminating the physical separation between the RNA synthesizing reaction and the RNA hybridizing reaction which the prior art rely upon to facilitate RNA fragmentation prior to contacting the immobilized probe array. The principle of operation underlying the

reusable device of **Marble** relies on retention of the immobilized template nucleic acid through many rounds of synthesis and removal of solution-phase *in vitro* transcripts. However, the suggested obvious device would seem to have no utility as a reusable construct because there is no explanation for how to regenerate bound probe without also removing the template which must be retained according to **Marble**. **Adams** relies on the synthesis of amplicons that remain bound to the solid support. Of course, this objective would be defeated by the production of solution-phase transcripts using the T7 promoter-primer immobilized to the instantly recited solid support bead. The principle of operation of **Hanninen** relies on distinguishing between hybridized probe immobilized to a microparticle, and unhybridized probe in the solution-phase – something eliminated in the suggested obvious construct, and in **Adams**. Finally, **Majlessi** provides no impetus for undoing the principle of operation underlying any of these references.

It should be clear from the foregoing that the suggested modification would inappropriately require a change in the principle under which the prior art inventions were designed to operate (*see* M.P.E.P. § 2143.01). Accordingly, Applicant believes the rejection is improper, and so requests withdrawal of the § 103 rejection of Claims 44-48, 50-52 and 55.

II. The Rejection of Claim 49 Under § 103(a)

Claim 49 stands rejected under 35 U.S.C. § 103(a) over the combined disclosure of the above-discussed six references, further in view of *J. Am. Chem. Soc.*, 121:2921-2922 (1999) ("**Fang**" hereafter). More particularly, the rejection relies on this seventh reference for teaching molecular beacon probes comprising fluorophore and quencher moieties.

The invention of Claim 49 would not have been obvious under § 103(a) in light of the cited reference combination for the following reasons. The teaching of **Fang** does not make up for the

deficiency in the remaining reference combination, or provide any reason for undoing the teaching of the primary and secondary references in view of the prior art (*e.g.*, the above-referenced article by Southern *et al.*,). The mere coincident appearance of key words in a single document does not support the suggested invention when the references themselves and the prior art provide a reasoned basis for maintaining the T7 promoter-primers and probes separate from each other. Accordingly, withdrawal of the rejection of Claim 49 under § 103(a) is respectfully requested.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

DEPOSIT ACCOUNT INFORMATION

Please charge any fees due in connection with this submission, including the fees due under 37 C.F.R. § 1.17 for a three-month extension of time, to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Respectfully submitted,

GEN-PROBE INCORPORATED

Dated: April 7, 2009

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